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EXAMINER	
SKIBINSKY, ANNA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	09/707,576	MAGNESS ET AL.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/18/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,14-26,28,32-44 and 46-61* is/are pending in the application.

4a) Of the above claim(s) *56-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14-26,28,32-44 and 46-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/06; 2/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Claim Amendments

Amendments to claims 1, 20, and 49-51 are acknowledged. Claims 11-13, 27, 29-30, and 45 are cancelled.

Newly submitted claims 56-61 are again withdrawn for being directed to an invention that is independent or distinct from the invention originally claimed. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57-61 are again withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-10, 14-26, 28, 32-44 and 46-55 are under examination.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-19, 47, 49, 50, and 51 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-19, 47, 49, 50, and 51 are drawn to a process for the classification of medical data of populations and the identification of a drug target by comparing genetic differences between two populations. The process for identifying the genetic differences

and the subsequent drug target, according to the claimed method, involves the application of algorithms and computations, that result in identification of said drug target, and therefore, involves the application of a judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims recite a practical application; i.e. recite a useful, concrete, and tangible result. See MPEP 2106, in particular, Section IV, for an explanation of a concrete, tangible and useful result.

Claims 1-19, 47, 49, 50, and 51 do not recite a tangible result. It is noted that applicants have amended claim 1 to recite "displaying the data for a user." However, this is neither a physical transformation of matter nor a concrete, tangible or useful result of the method because "the data" is the initial medical histories and test results, not the result of the computational methods of the claimed steps. A tangible result requires that the claim must set forth a practical application to produce a real-world result. Examples of a "real-world result" include a physical transformation of matter, or a step of communicating the result in a TANGIBLE format to a user; e.g. by outputting or displaying the result of the method. It is noted that the last step of the methods recited in claims 1 and 20 is one of identifying a drug target. Identification of a drug

target is both concrete and useful; however, as the information is not communicated to a "user", it is not a tangible result which flows from the claimed method steps. Applicant is reminded that any amendment must be fully supported and enabled by the originally filed description.

As the claims do not recite a physical transformation of matter OR a concrete, tangible and useful result, they are not directed to statutory subject matter.

Response to Arguments

2. Applicant's arguments filed 12/18/2007 have been fully considered but they are not persuasive.

3. Applicants remark (Remarks, page 16) that claims have been amended to include a step of displaying the data for a user.

4. While the examiner appreciates applicant's attempt to comply with her suggestion, it is noted that the amended step is not a concrete, tangible or useful result of the computational method because "the data" which is displayed is the initial medical histories and test results, not the *result* of the computational steps recited in the claims.

5. It is unclear whether the remarks running from the last paragraph on page 16 through page 17 are intended to address the statutory rejection in addition to the enablement rejection. In the event that the remarks are intended to address the rejection under 35 USC 101, then the following response applies: In response to the argument that the claimed methods are "short-cuts" it is noted that the rejection is not one of enablement, anticipation nor obviousness. An argument that a method is an improvement over the prior art MAY be persuasive in overcoming a rejection under 35

USC 112, 102, or 103. However, the mere fact that a method "improves" on what is known does not render the CLAIMED invention statutory, thus the argument, as applied to the statutory rejection, is moot.

6. The "definition" of screening set forth on page 17 of the response makes it clear that "screening" is not intended to be a physical step, therefore this argument is also moot as it applies to the statutory rejection.

Claim Rejections - 35 USC § 112-1st Paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT

2. Claims 1-10, 14-26, 28, 31-44 and 46-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state

of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must identify a drug target for an unspecified biological condition from data related to identified genetic variations between ARA and ARAU subpopulations. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The disclosure (see for example, page 25, line 19 through page 30, line 8) sets forth steps that are taken to analyze a population and define affected status, risk factors, and the characterization of the ARA, ARU, and URU phenotypes. The disclosure does not provide any guidance as to what procedures or practices using identified genetic variations between ARA and ARAU subpopulations that result in the identification of a drug target for "any" biological condition.

c) The disclosure does not provide any examples wherein a drug target was identified.

d) The nature of the invention, drug target identification, is complex.

e) The prior art teaches studies of hepatitis C, and it is acknowledged that the genetic basis for many specific diseases is known. It is noted that even where the genetic basis of a disease is "known," in many instances, the etiology of a disease is such that the "target" for treatment is not the gene itself. However, the claims are not limited to a specific disease or disorder, and it is well known in the art that the genetic

basis for all "biological conditions" are not known. The prior art is silent in regards to methods or procedures wherein a drug target associated with an unspecified biological condition is identified through data related to genetic variations between ARA and ARU subpopulations, wherein no prior knowledge of a relationship between said target and said biological condition is available.

f) The skill of those in the art of drug target identification is high.

g) The unpredictability of identifying a drug target for an unspecified biological condition from data related to genetic variances is high, as the target for treatment (e.g. a drug) is not necessarily a gene, or a gene product, per se. For example, it is well known in the art that down- or up-regulation of expression of a protein (gene product) may cause a disorder or disease. Protein expression levels are controlled by a number of factors, including regulatory elements which bind to the gene itself, and inhibitors, activators, co-factors, etc. which control protein activity. This is supported by the instant specification, on page 11. Any of these factors may, in fact, be the "target" which needs to be addressed for appropriate treatment of the disease or disorder. Assuming one is, in fact, able to identify a gene product, and thus a (presumably) mutated gene (variance) which is "involved" in a disease etiology, one can not then simply assume that the gene or its product is a "target" for treatment. Without further research to determine the actual causative element for the disease or disorder, or symptoms thereof, one would not know WHAT to target. If protein expression is down-regulated because the regulatory region of the gene is mutated such that transcriptional factors cannot bind appropriately, then the "target" can not be treated with a "drug;" one would

have to actually alter the genetic sequence itself. It is noted that in this case, the disease itself may still be treated; perhaps by administration of higher levels of the protein; however, even if the protein were to be considered a "drug," the "drug" is not directed to a "target." Further, it is well known in the art that many diseases and disorders are not due to a single gene mutation (variance), but are the result of a constellation of reactions or interactions between several genes and/or gene products. One may identify a single mutated gene which is "involved" in a disease or disorder, but more research would be required to determine and/or confirm whether that gene (and mutation) are indeed causative for the disease or disorder symptoms before one can even begin to determine what an appropriate "target" for a drug would be. As it is well known that many factors are involved in disease etiology, discovery of a mutated gene does not lead directly to identification of a drug target, but requires further experimentation. Thus, the degree of unpredictability for identifying a gene target is high.

h) The claims are broad in that they are drawn to identification of a drug target for an unspecified biological condition from data related to genetic variances, wherein the genetic variances are not necessarily known to be correlated to a particular condition.

The skilled practitioner would first turn to the instant disclosure for guidance in using the claimed invention. However, the disclosure lacks clear guidance for how to identify a drug target for an unspecified biological condition which is merely related to genetic variances, using only the claimed method steps. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not disclose

methods or procedures for identifying a drug target for a given biological condition based on genetic variations between ARA and ARU subpopulations, wherein no prior knowledge of causative elements for the biological condition is available. Finally, due to the high level of unpredictability in the art set forth above, said practitioner would turn to trial and error experimentation to identify a drug target for a given biological condition using said data. Such amounts to undue experimentation.

For the reasons set forth above, the claims in the instant application to identifying the drug target associated with a selected biological condition are not enabled.

Response to Arguments

3. Applicant's arguments filed 12/18/06 and 2/22/2007 have been fully considered but they are not persuasive.

For purposes of brevity, the examiner's remarks refer only to independent claims. However, it is noted that all dependent claims are also considered non-enabled for the same reasons set forth as for the independent claims.

Applicants reiterate (page 18, lines 7-13, of the Remarks 2/22/2007) that the present application provides extensive guidance to allow one of ordinary skill in the art to obtain a target (such as polypeptide) that is within the scope of the claims and by following the guidance, applicants have developed a target and a drug.

The specification teaches (page 10, line 26 to page 11, line 10) the use of PCR to amplify the coding regions of a set of candidate genes and then comparing each patient's candidate gene sample sequence to a reference sequence to identify all

sequence mutations and variants associated with a chosen phenotype. It is noted that claim 1 does not recite PCR or any actual steps of performing genetic tests, thus the genetic data analyzed in claim 1 does not necessarily have any correlation or relationship to the "condition" of interest. Thus, arguments with regard to genetic testing and PCR are not persuasive as applied to claim 1. Claim 20 does recite genetic testing, and it is acknowledged that PCR is a well-known technique for obtaining nucleotide sequences. It is further acknowledged that, while such analysis may be time-consuming, it would not require undue experimentation to identify one or more genetic differences between two populations. However, in the absence of any correlation between medical status and genetic tests, and/or in the absence of further testing and research, it would require undue experimentation to determine whether any genetic variation between the populations is indeed correlated to a biological condition, It is noted that claim 20, unlike claim 1, recites specific limitations with regard to medical/risk status of the sub-populations such that the genetic variations are necessarily correlated to both a particular disease AND to specific risk factors involved in disease etiology. Claim 1 does not recite such limitations, therefore applicant's arguments with regard to genetic testing are not persuasive with regard to claim 1. Applicant's arguments with regard to the example are not persuasive as the example pertains to a specific disease (hepatitis C). The claims are not limited to a specific disease; in fact, claim 1 is directed to a "biological condition" which is broadly defined by the specification on page 8 as a "biological state, disease, physiological condition, or the like. " Using this definition, the ARA population may be healthy (physiological condition) individuals while the ARU

population may be individuals deemed to be "unhealthy" (i.e. "at risk" for being healthy but are not) for any reason! It would indeed be possible to determine genetic variations between these populations, but the information would be meaningless. Even one highly skilled in the art would have no idea how to identify a "drug target" for a biological condition which is "healthy."

Applicants argue that Examiner provides no basis for saying that the instantly claimed invention would entail an unpredictable amount of experimentation (Remarks page 18, lines 23-25).

In response, while the specification does provide guidance for how to develop a drug when a polypeptide is KNOWN to be the target (e.g. page 8), the specification does not provide any guidance for how IDENTIFY a drug target based ONLY on identification of genetic variations between ARA and ARU (and sometimes URU) populations. In fact, the specification teaches on page 11 that mutations that are "identifying markers" for drug target genes are discovered through a combination of informatics based and statistical genetics analysis. In order to do so, the specification discloses that a candidate sample sequence is compared to *a reference sequence*, NOT by generally comparing random genetic information from different, albeit selected, populations. The instant claims do not limit the "analysis" to any particular type, nor do the claims recite comparison of candidate gene samples to any reference sequence. Page 11 also discloses that mutations can be analyzed on the basis of functionality and "bin" frequencies. No limitations with regard to "functionality," binning or frequency analysis are recited in the instant claims. Thus, even where the claims recite a disease

and genetic testing, as in claim 20, the specification does not teach, using only the method steps RECITED IN THE CLAIMS, how to determine whether any genetic variation found is indeed correlated to the disease, nor how to identify from the variation information ONLY, what a "target" for a drug or treatment should be. Applicant is reminded that while enablement is assessed based on the general knowledge in the art and the disclosure of the specification, limitations from the specification can not be read into the claims. Thus, the arguments with regard to specific steps and limitations which are not reflected in the claims are not persuasive for the reasons set forth above.

As supported by the instant specification, it is known that many diseases such as various cancers are caused by up-regulated genes but neither the gene nor the (overexpressed) polypeptide are the actual cause of the cancer. In fact, in many cases, there is no mutation in the genetic code causing the cancer. It is well known that there are adeno and retroviruses that cause changes in regulation of the expression of certain genes which thus results in cancer in mammals, but do not result in variation/mutation in the encoding gene sequence itself. In these cases, identification of a "variation" in the genetic code would not necessarily lead one to identify the protein as a drug target, nor would knowledge of which protein is upregulated (and by association, which gene) lead one to a "correlation" with a particular genetic variation. Thus, for diseases which are caused by an "outside agent," for which there is no associated genetic "variation," such as these cancers, it would be impossible to identify any drug target using the claimed method steps, therefore, the examiner maintains that identification of a drug target would require undue experimentation.

Applicants argue (Remarks, page 19, lines 16-25) that the invention is novel in that previously known methods are applied in a new way. Applicants argue that it is the intention of the invention is to discover the phenotype of people who are naturally resistant to the disease or condition.

In response, it is noted that the instant claims do not recite any "new way" of applying previously known methods of sample collection, DNA sequencing, or sequence comparison. The steps of data analysis recited in the claims are not limited to any particular algorithm, model, etc., therefore the arguments are not persuasive for either the actual steps recited nor for data analysis. Furthermore, the instant claims do not recite any limitations for discovering the phenotype of people who are naturally resistant to a disease or condition, but recite classification of people into groups based on phenotype. Currently the claims are extremely broad and the phenotypic classification is not limited the discovery of any special phenotype attributed to resistance. Rather, the claims encompass the classification of people with any selected phenotypic differences of interest. Claim 1, for example, may encompass fair people (medical history) who develop freckles (condition) after exposure to sunlight (medical tests) (ARA) and fair people that do not develop freckles (ARU). Neither the specification nor the prior art disclose how one is to identify a drug target after comparison of the genetic differences between freckled and unfreckled populations. Even in light of the instant specification's disclosure for statistical analysis, frequency determination and "binning," one skilled in the art would not be able to identify a "drug target" based on genetic variation between these populations.

Applicants cite the reference by Drew et al. (Remarks, pages 19-20) entitled "Genomic science and the medicine of tomorrow," which teaches that 417 drug targets "were not discovered by knowing completely the pathways that were relevant in diseases," (Remarks, page 19, lines 26-30)

In response, it is admitted that while helpful, knowledge of pathways are not required in order to identify a drug target. What is required is some knowledge of a correlation between a drug target and a disease or other biological condition. In fact, in the two sentences immediately following that cited by applicants, Drew states that the 417 targets "were found empirically by chemical and pharmacological methods" and "[t]he distribution of these targets is patchy," (Drew, col. 3, lines 41-48). Further, Applicants cite (Remarks, page 20, lines 7-9) from Drew that "nearly half the targets remain unknown" thus admitting that targets may remain unknown, even for disorders with a known genetic basis. This supports the examiner's position that identification of a drug target based ONLY on genetic variations between two populations is not enabled in the absence of further information and/or experimentation. In the absence of such information/experimentation, such as that taught by Drew, one must guess at the identity of drug targets.

Applicants argue (Remarks, page 21, lines 23-29) that a drug target flows form identification of genetic differences and (Remarks, page 22, lines 15-17) that the mere fact that a functionally relevant biological difference between ARA and ARU group is identified in a gene indicates that said gene is a drug target.

In response, it is noted that the instant claims do not recite the identification of a "functionally relevant" biological difference between ARA and ARU groups. Although not specifically argued, a "functionally relevant" biological difference is assumed to mean a "functionally relevant" biological difference pertaining to a disease. Currently the claims recite "using the data related to identified genetic variations" between ARA and ARU groups. There is no indication in the claims that the identified variations are functionally relevant to the disease or biological condition and therefore could be any genetic variations between the two groups.

Applicants argue (Remarks, page 23, last paragraph) that Drs. Lesser and Myers refute the statement by Examiner and point to the affidavits.

In response, please see the replies to affidavits below.

Response to Amendment

The affidavit of Dr. Richard M. Myers, under 37 CFR 1.132, filed 12/18/2006 has been fully considered but is not persuasive for the following reasons:

In response to Dr. Myers' documentation of personal expertise (paragraphs 1-2 on pages 1-2) It is acknowledged that Dr. Richard M. Myers is an internationally recognized scientist and one of skill in the art in the field of genetics.

Dr. Myers states his opinion (paragraph 3) that the methods described in the instant application and state of the art support the enablement of the claimed invention.

In response, Dr. Myers has presented his opinion but has not produced evidence to support a basis for enablement of the instantly claimed invention.

Dr. Myers states that the amount of genetics work required in the instantly claimed invention is not unpredictable as asserted by the Examiner but that according to his experience as an acknowledged expert in his field, the work is required is predictable. Dr. Myers states that he has been required to predict the amount of effort in his proposals and fund agencies.

In response, it is noted that funding of a project achieved with a successful grant proposal, as those referred to by Dr. Myers (Affidavit, paragraph 4), is not equivalent to predictable success of a research project nor is a "successful" proposal evidence that a CLAIMED invention is enabled or patentable. Applicant is respectfully reminded that a patent application is not the same as a grant proposal.

Dr. Myers states (paragraph 5) that he disagrees with the Examiner's assertion that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete."

In response, it is acknowledged that timeliness alone does not render a claim nonenabled. However, while Dr. Myers' opinion as an expert in his filed is recognized, it is noted that he does not cite or otherwise provide evidence that the identification of a drug target based ONLY on knowledge of genetic differences between two populations would not involve undue experimentation.

Dr. Myers states (paragraph 6) that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism, and to determine whether that mutation corresponds to phenotypic characteristics of a subpopulation. It is routine to identify genetic mutations associated with phenotypic characteristics without

previous knowledge of a relationship to the biological condition. The examiner agrees that it is possible, and in fact has been routine for many years, to identify a mutation associated with a phenotype where no previous correlation between the mutation and the phenotype was previously known. If the correlation were previously known, such research would not be necessary! However, it is noted that in many cases, it is not possible to identify mutation(s) associated with a disease, nor specifically those which cause a disease. In these cases, it would be impossible to identify a drug target based on genetic variation between populations.

For example, even as recently as 2004, in the paper of Ntais et al. (American Journal of Epidemiology, vol. 159 (2004) pages 527-536) medical data, back ground, ethnicity, and genetic differences are assessed (page 530, col. 1, lines 32-37 and col. 2, lines 31-44) for those who develop Alzheimer's but the genetic mutation directly responsible for the disease has not been identified (Ntais et al., page 530, section "Disease"). Furthermore, the authors note that anti-inflammatory drugs used to treat arthritis as well as physical exercise, diet and B vitamins are still used to reduce the risk of Alzeimer's disease (page 530, col. 1, section "Disease", lines 14-20). These drugs are not chosen based on any particular "target" identified from an analysis of genetic variations between affected and unaffected populations of elderly people (e.g. those "at risk). In fact, despite the studies of polymorphisms associated with Alzheimer's disease, the identification of the polymorphisms responsible for the disease, from which drug targets would be "identified" in the claimed methods, still requires trial and error experimentation (Ntais et al., page 530, col. 2, section "Meta-Analsis Methods").

Dr. Myers states (paragraph 7) that it would not require undue experimentation to identify a protein or regulatory region that correlates with the observed genetic difference.

In response, genetic differences between two populations correlate with a multitude of proteins and regulatory regions. Determining which of these is a "drug target" requires undue experimentation as one skilled in the art would have to guess at which is truly causative of disease symptoms, and would have to perform further research to confirm that guess.

Dr. Myers states (paragraph 8) that it is his belief that the methods of the claimed invention are broadly applicable, beyond infectious disease.

In response, it is noted that the rejection does not make any statements with regard to "infectious" diseases. It is further noted that no evidence is provided to support Dr. Myers' statement. The examiner maintains that even based on known genetic differences in populations, the identification of a drug target associated with an unspecified biological "condition," as recited in the claims, requires undue experimentation for the reasons set forth above.

Dr. Myers states (paragraph 9) that entire classes of important drugs act on polypeptide drug targets and that there exist polypeptide therapies where a peptide is the drug itself.

In response, it is noted that while a polypeptide may indeed be a drug or a drug target, the claims do not recite any limitations with regard to polypeptides, but only recite identifying a drug target based on *genetic* variations between populations.

Dr. Myers states (paragraph 10) that applicants describe general methods to identify functional mutations differently associated with the ARA and ARU groups and that associated methods for identifying genetic mutations such as those described have been known in the art since 1990.

In response, it is noted that it is well known in the art that the identification of a mutation is not the equivalent to identification of a drug target associated with a particular biological condition. Further, the claims do not recite any limitations with regard to functional mutations.

Dr. Myers states (paragraph 11) that it is the comparison of the observed genetic differences with the database to pinpoint the modified region and identify the function that leads directly to identification of a drug target.

In response, it is noted that the claims do not recite "pinpointing the modified region associated with a particular disease," but only recite "identifying genetic variations" (claim 1, lines 15-16) between two populations that have been classified based on phenotypic differences. The identification of genetic differences is not equivalent to identification of a region associated with a particular disease. Further more, as in the case with Alzheimer's disease exemplified above, even polymorphic regions associated with a particular disease do not necessarily lead to the identification of a drug target.

The affidavit of Dr. Cammie Lesser, under 37 CFR 1.132, filed 12/18/2006 has been fully considered but is not persuasive because:

In response to Dr. Lesser's documentation of personal expertise (paragraphs 1-2 on pages 1-2) It is acknowledged that Dr. Lesser is an internationally recognized scientist and one of skill in the art in medicine and the field of genetics.

Dr. Lesser states (paragraph 4) that it is routine to identify a mutation without knowledge of the underlying disease mechanism and to determine whether that mutation corresponds to the phenotypic characteristics of a population.

In response, the claims do not recite identifying a mutation and determining whether that mutation corresponds to the phenotypic characteristics of a population. On the contrary, the claims recite identifying genetic differences (not a mutation) between two populations with phenotypic *differences* (one affected group and one unaffected group).

Dr. Lesser states (paragraph 6) that methods used to identify mutations in genes and to correlated these mutations with functional effects such as modification of protein amino acid sequence, are "methods routinely used".

In response, it is acknowledged that association of a genetic mutation with a modified amino acid sequence are indeed well-known and "routine." However, due to the redundancy in the coding of amino acids, it is equally well known that mutation in a particular codon does not necessarily result in a change in a protein sequence. In addition, it is well-known in the protein arts that while an amino acid change MAY result in a structural and/or functional difference in a protein, this is not always the case. Conservative changes often result in no observable difference in the function of a protein. Any change in an amino acid will result in a structural difference, but often the

difference is so subtle as to be observable only by crystallization, X-ray diffraction, etc. Thus, association of a genetic mutation with a *functional* effect is not necessarily routine. Further, even where a genetic mutation is successfully correlated with a "functional" effect, this does not automatically lead to identification of a drug target for reasons set forth above.

Dr. Lesser states (paragraph 7) that it is entirely feasible and within ordinary skill in the art to identify genetic differences that are correlated with the affected versus unaffected phenotype.

In response, it is noted that many genes that may be correlated with a phenotype/biological condition. In addition, any two populations which are not controlled for gender, race, etc. would be expected to have many genetic variations between them. Thus, while Dr. Lester's statement is correct, it is noted that the genetic differences identified in the claims are not necessarily those associated with or causative of a disease.

Dr. Lesser states an opinion (paragraph 8), that it is highly unlikely that few if any drugs have been identified by "sorting out 1000's of targets present in most organisms."

In response, it is noted that SOME knowledge of a disease etiology as correlated to a particular "genetic variation" is required to identify a drug target in order to avoid "sorting out 1000's of targets." As set forth above, merely identifying genetic variations between affected and unaffected populations does not necessarily lead to identification of a drug target. MANY variations may be identified, in which case, one would indeed have to "sort" through all of them in order to determine which, if any, is actually

correlated to presence of a disease. Upon that determination, and assuming that the disease actually is correlated with a mutation, one would than have to determine whether the gene itself, an encoded protein, or some other factor is an appropriate "target." The examiner maintains that this is not routine and represents undue experimentation.

Dr. Lesser states (paragraph 9) that the claimed method is a short cut to drug discovery through the identification of the observed genetic differences (e.g. point mutation, deletion, insertion) between the ARU and ARA groups which leads directly to identification of a drug target.

In response, applicants do claim "identifying genetic variations" (claim 1, lines 15-16) between two populations that have been classified based on phenotypic differences. The identification of genetic differences is not equivalent to identification of a region associated with a particular disease. As in the case with Alzheimer's disease (see Ntais et al. cited above), even identification of polymorphic regions associated with a particular disease do not necessarily lead to the identification of a drug target

The affidavit of Dr. Shawn Iadonato, filed 2/22/07 contains the same statements as the affidavit of 12/1/8/2007, therefore the two affidavits are treated as one in the following remarks.

The affidavit of Dr. Shawn Iadonato, under 37 CFR 1.132, filed 12/18/2006 and 2/22/06 have been fully considered but is not persuasive because:

In response to Dr. Shawn Iadonato's documentation of personal expertise (paragraphs 1-3 on pages 1-2). It is acknowledged that Dr. Lesser is an internationally recognized scientist and one of skill in the art in the field of genetics.

Dr. Iadonato states that by following the methods of the present invention in a hepatitis C study, more than one drug target was identified, wherein the first was identified in an extremely short period of laboratory work.

In response, applicant is reminded that instant claim1 is not limited to a disease or a disorder. While instant claim 20 does recite a disease, it does not recite a specific disease, nor specifically Hepatitis C. It is further noted that the ARA/ARU populations of claim 1 are classified by phenotypic characteristic and not disease or disorder. Unlike the example set forth by Dr. Iadonato, the claimed populations are not limited to be those exposed to a virus.

Dr. Iadonato states that a single cycle of data input, review and analysis according to the invention led directly to this drug discovery.

In response, the instant claims are extremely broad and recite the identification of a drug target for an unspecified biological condition (e.g. claim 1) or disease (e.g. claim 20) from the identification of genetic differences between two populations. The claims are not limited to the identification of a particular disease such as Hepatitis C nor are they directed to a method of drug discovery. It is noted that the modified protein disclosed by Dr. Iadonoto is considered a DRUG, not a drug TARGET. Further, the steps referred to on page 10 of the specification as the "single cycle" are not those reflected in the claims. As set forth above, the instant claims do not recite comparison

to *a reference sequence*, functional analysis, frequency analysis, or any other specific statistical analysis.

Dr. Iadonato states (paragraph 11) that what applicants have disclosed and claimed is a new method of target and drug discovery. The drug discovered for Hepatitis C was based on studying ARU populations who already express a version of the drug and enjoy the beneficial effects of having it in their system.

In response, the instant claims are not drawn to "studying ARU populations who already express a version of the drug" but are directed to identification of a drug target based on genetic variations between broadly defined populations. As the claims are not directed to a product, nor do they recite any particular sequences, the arguments with regard to SEQ ID NO: 48 are moot.

Contrary to the assumption made in paragraph 13, granting of "special status" in a related application does not confer enablement on the instant claims. Further, applicant is reminded that timeliness is not a factor in assessing enablement. While applicant is congratulated for discovering a drug in a relatively short time, the fact that he did so does not enable the CLAIMED methods.

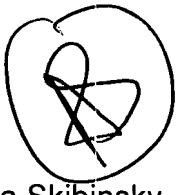
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Anna Skibinsky, PhD

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
5/14/07